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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/570,588	01/22/2007	Martin Andrew Crockard	30986/40924	7390

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EXAMINER	
SHAW, AMANDA MARIE	
ART UNIT	PAPER NUMBER
1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/570,588	CROCKARD ET AL.	
	Examiner	Art Unit	
	Amanda Shaw	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-8 and 10-14* is/are pending in the application.

4a) Of the above claim(s) *6,7 and 10-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,8 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *3/3/2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/22/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed June 14, 2010. This action is made NON FINAL.

Claims 1-2, 5-8, and 10-14 are currently pending.

Claims 1, 5, 8, 14 have been amended.

Claims 6-7 and 10-13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on February 16, 2010.

Claim Rejections - 35 USC § 112 1st paragraph

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 5, 8, and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the Invention

The claims are drawn to a method for the detection of the presence of or the risk of breast cancer in a patient. The method comprises: (i) isolating a sample of the patient's genome; and (ii) detecting the level of expression of the gene comprised within the sequence identified herein as SEQ ID NO: 1. The "wherein" clause states that increased expression of the gene in the sample, compared to the level of expression of the gene in normal control breast tissue indicates the presence of or the risk of breast cancer. The nature of the invention requires a reliable association between the level of expression of the gene and the presence of or the risk of cancer.

Scope of the Claims:

The claims require a step of isolating a sample of the patient's genome. This broadly encompasses isolating ANY type of sample (i.e., breast tissue, lung tissue, brain tissue, hair, blood etc).

Claim 8 requires detecting the level of expression of the gene comprised within the sequence identified as SEQ ID NO: 1 by performing an in vitro hybridization assay with the sample of the patients genome and ANY isolated polynucleotide comprising at least 15 consecutive nucleotides of SEQ ID NO: 1 or its complement.

Teachings in the Specification and Examples:

Here it is noted that the gene located in SEQ ID NO: 1 has the sequence of SEQ ID NO: 2. This gene is referred to in the specification as DD11. Further it is noted that SEQ ID NO: 1 is 513 base pairs long and the gene located within SEQ ID NO: 1 is only 138 bp long.

The specification (page 8) teaches that differential gene expression between matched pairs of normal mammary and tumor tissue from the same donor was carried out. The specification asserts that a number of differentially expressed gene fragments were isolated and one of these fragments, referred to herein as DD11, was significantly up regulated in breast tumor tissue samples from a number of donors. The specification (page 11) teaches that sequence analysis followed by database interrogation determined that DD11 was not homologous to known genes or proteins in the EMBL and SWISSPROT databases, therefore it was regarded as potentially novel. However it was 100% homologous, after removal of the poly-A tail, to a clone (RP11875011) from chromosome 8 of the human genome (Accession Number AC107959).

The specification (page 11) teaches that the DD11 fragment was further screened using cDNA populations derived from a number of matched breast tumor tissues donated by other patients. Of the donor samples screened, 6 out of 9 exhibited notable increases in expression, confirming DD11 to be a putative molecular marker for the presence of breast tumor (FIG. 1). This analysis was substantiated by the molecular signature analysis of all currently available matched breast tissue samples, as follows:

Increased in tumor: 10 out of 19 (52.6%)
Increased in normal: 1 out of 19 (5.3%)
No discernable difference: 7 out of 19 (36.8%)
No expression evident: 1 out of 19 (5.3%)

The instant specification asserts that DD11 was "significantly" up regulated in breast tumor tissue samples from a number of donors however the specification does not actually provide the expression levels that were obtained for each patient. Further the specification does not define the parameters they used to determine that a particular result was "significantly" up regulated. Further the specification does not provide any p values indicating that there is a statistically significant association between increased DD11 expression and the presence of or risk of breast cancer. The instant specification only teaches that DD11 was increased in breast tumor tissue samples in comparison to non cancerous breast tissue samples, yet the claims encompass a method for detecting the presence of or the risk of breast cancer by detecting the level of expression of DD11 in ANY type of sample (breast tissue, heart tissue, liver tissue, hair, urine, etc.). Regarding claim 8 the specification does not teach how it is possible to use ANY isolated polynucleotide comprising at least 15 consecutive nucleotides of SEQ ID NO: 1 or its complement to detect the level of expression of the gene within SEQ ID NO: 1 particularly since SEQ ID NO: 1 is 513 base pairs long and the gene is located within SEQ ID NO: 1 from nucleotides 150-287. In other words the specification does not teach how it is possible to use an isolated polynucleotide consisting of nucleotides 1-15 of SEQ ID NO: 1 to detect the level of expression of the gene within SEQ ID NO: 1 because the isolated polynucleotide does not even hybridize to the actual gene, rather is hybridizes to sequences upstream from the gene.

State of the Art and the Unpredictability of the Art:

The level of skill in the art is deemed to be high. However the unpredictability with regard to correlating the expression level of a gene with breast cancer is even higher. The unpredictability is discussed below.

The unpredictability of correlating a gene expression level to a phenotypic quality is known in the art. For example Lucentini (The Scientist 2004 Vol 18 pages 1-3) teaches that reproducible gene-disease associations are few and far between (page 2). Lucentini teaches that it is strikingly common for follow-up studies to find gene- disease associations wrong (page 2). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a disease there is only roughly a one-third chance that the study will reliably confirm the finding (page 2). Lucentini teaches that bigger sample sizes and more family-based studies, along with revised statistical methods should be included in the gene association studies (page 3). These teachings are relevant to the instant invention because such a small initial sample size was used (n=19) and because the results have not been validated in other populations.

Because the claims require correlating any level increased expression with the presence of or the risk of breast cancer, it is relevant to point out that Cheung (Nature Genetics 2003 Vol 33 pages 422-425) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) (p.422, last paragraph; Fig 1). The data indicates that, for example, expression of

ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). It is thus unpredictable as to whether or not any level of increased expression is associated with the presence of or the risk of breast cancer.

Since the specification does not provide any p values it is highly unpredictable if there is a statistically significant association between increased DD11 expression and the presence of or risk of breast cancer. Thisted (The University of Chicago 1998) teaches that p values are needed to determine whether superior results obtained in a particular study are really superior or if they occurred by chance (page 1). Thisted teaches that it has become scientific convention to say that p values exceeding 0.05 are not statistically significant. Since the instant specification does not provide any p values it's not certain if the findings are superior or if they occurred by chance.

Because the claims encompass detecting the expression level of DD11 in ANY type of sample it is relevant to point out the unpredictability in comparing gene expression among different tissues. While the genetic information is the same in all tissues that constitute a multicellular organism, the expression of functions encoded by the genome varies significantly in different tissues. In fact Whitehead (Genome Biology 2005 Vol 6 Issue 2 Article R13) teaches that variation in gene expression is extensive among tissues (abstract). Whitehead further teaches that many different cancers have unique tissue specific patterns of gene expression (page 1, col 2). Here it is noted that with regard to the breast cancer patients the specification does not teach that DD11 was significantly up regulated in other types of tissues samples (i.e. non breast tissue

samples) obtained from those patients. Thus in the absence of evidence to the contrary it is highly unpredictable if it is possible to detect breast cancer by detecting the expression level of DD11 in non breast tissue samples.

Quantity of Experimentation:

In the instant case a large amount of experimentation would be required to make and use the invention as broadly claimed. For example it would require validating the findings in the specification using a larger population with thousands of samples to demonstrate a statistically significant association between the increased expression of DD11 and breast cancer. Such experimentation would be extensive. The results of performing such methodology are highly unpredictable. The specification has provided only an invitation to experiment.

Conclusions:

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the guidance provided by the applicant and the specific examples, it is the conclusion that an undue amount of experimentation would be required to make and use the invention.

Response To Arguments

3. In the response filed June 14, 2010, the Applicants stated that they have amended the claims to be commensurate in scope with the invention that the Office has acknowledged to be enabled.

The claims as amended have been fully considered however after further consideration new enablement issues have been raised. These issues are discussed above.

Conclusion

4. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda Shaw whose telephone number is (571)272-8668. The examiner can normally be reached on Mon-Thurs 8:00 TO 6:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Amanda Shaw/
Examiner 1634